Effect of an educational intervention on therapeutic inertia in neurologists with expertise in multiple sclerosis: a randomized clinical trial

Saposnik, Gustavo ; Grueschow, Marcus ; Oh, Jiwon ; Terzaghi, Maria A ; Kostyrko, Pawel ; Vaidyanathan, Shruthi ; Nisenbaum, Rosane ; Ruff, Christian C ; Tobler, Philippe N

Abstract: Importance: Therapeutic inertia (TI) is the failure to escalate therapy when treatment goals are unmet and is associated with low tolerance to uncertainty and aversion to ambiguity in physician decision-making. Limited information is available on how physicians handle therapeutic decision-making in the context of uncertainty. Objective: To evaluate whether an educational intervention decreases TI by reducing autonomic arousal response (pupil dilation), a proxy measure of how physicians respond to uncertainty during treatment decisions. Design, setting, and participants: In this randomized clinical trial, 34 neurologists with expertise in multiple sclerosis (MS) practicing at 15 outpatient MS clinics in academic and community institutions from across Canada were enrolled. Participants were randomly assigned to receive an educational intervention that facilitates treatment decisions (active group) or to receive no exposure to the intervention (usual care [control group]) from December 2017 to March 2018. Participants listened to 20 audio-recorded simulated case scenarios as pupil responses were assessed by eye trackers. Autonomic arousal was assessed as pupil dilation in periods in which critical information was provided (first period [T1]: clinical data, second period [T2]: neurologic status, and third period [T3]: magnetic resonance imaging data). Data were analyzed from September 2018 to March 2020. Interventions: The traffic light system (TLS)–based educational intervention vs usual care (unexposed). The TLS (use of established associations between traffic light colors and actions to stop or proceed) assists participants in identifying factors associated with worse prognosis in MS care, thereby facilitating the treatment decision-making process by use of established associations between red, green, and yellow colors and risk levels, and actions (treatment decisions). Main outcomes and measures: Pupil assessment was the primary autonomic outcome. To test the treatment effect of the educational intervention (TLS), difference-in-differences models (also called untreated control group design with pretest and posttest) were used. Results: Of 38 eligible participants, 34 (89.4%) neurologists completed the study. The mean (SD) age was 44.6 (11.6) years; 38.3% were female and 20 (58.8%) were MS specialists. Therapeutic inertia was present in 50.0% (17 of 34) of all participants and was associated with greater pupil dilation. For every additional SD of pupil dilation, the odds of TI increased by 51% for T1 (odds ratio, 1.51; 95% CI, 1.12-2.03), by 31% for T2 (odds ratio, 1.31; 95% CI, 1.08-1.59), and by 49% for T3 (odds ratio, 1.49; 95% CI, 1.13-1.97). The intervention significantly reduced TI (risk reduction, 31.5%; 95% CI, 16.1%-47.0%). Autonomic arousal responses mediated 29.0% of the effect of the educational intervention on TI. Conclusions and relevance: In this randomized clinical trial, the TLS intervention decreased TI as measured by pupil dilation, which suggests that individual autonomic arousal is an indicator of how physicians handle uncertainty when making live therapeutic decisions. Pupil response, a biomarker of TI, may eventually be useful in medical education. Trial registration: ClinicalTrials.gov Identifier: NCT03134794

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Original Investigation | Medical Education

Effect of an Educational Intervention on Therapeutic Inertia in Neurologists With Expertise in Multiple Sclerosis

A Randomized Clinical Trial

Gustavo Saposnik, MD, MPH, PhD; Marcus Grueschow, PhD; Jiwon Oh, MD, PhD; Maria A. Terzaghi, RPh; Pawel Kostyrko, MD; Shruthi Vaidyanathan, BSc; Rosane Nisenbaum, PhD; Christian C. Ruff, PhD; Philippe N. Tobler, PhD

Abstract

IMPORTANCE Therapeutic inertia (TI) is the failure to escalate therapy when treatment goals are unmet and is associated with low tolerance to uncertainty and aversion to ambiguity in physician decision-making. Limited information is available on how physicians handle therapeutic decision-making in the context of uncertainty.

OBJECTIVE To evaluate whether an educational intervention decreases TI by reducing autonomic arousal response (pupil dilation), a proxy measure of how physicians respond to uncertainty during treatment decisions.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial, 34 neurologists with expertise in multiple sclerosis (MS) practicing at 15 outpatient MS clinics in academic and community institutions from across Canada were enrolled. Participants were randomly assigned to receive an educational intervention that facilitates treatment decisions (active group) or to receive no exposure to the intervention (usual care [control group]) from December 2017 to March 2018. Participants listened to 20 audio-recorded simulated case scenarios as pupil responses were assessed by eye trackers. Autonomic arousal was assessed as pupil dilation in periods in which critical information was provided (first period [T1]: clinical data, second period [T2]: neurologic status, and third period [T3]: magnetic resonance imaging data). Data were analyzed from September 2018 to March 2020.

INTERVENTIONS The traffic light system (TLS)–based educational intervention vs usual care (unexposed). The TLS (use of established associations between traffic light colors and actions to stop or proceed) assists participants in identifying factors associated with worse prognosis in MS care, thereby facilitating the treatment decision-making process by use of established associations between red, green, and yellow colors and risk levels, and actions (treatment decisions).

MAIN OUTCOMES AND MEASURES Pupil assessment was the primary autonomic outcome. To test the treatment effect of the educational intervention (TLS), difference-in-differences models (also called untreated control group design with pretest and posttest) were used.

RESULTS Of 38 eligible participants, 34 (89.4%) neurologists completed the study. The mean (SD) age was 44.6 (11.6) years; 38.3% were female and 20 (58.8%) were MS specialists. Therapeutic inertia was present in 50.0% (17 of 34) of all participants and was associated with greater pupil dilation. For every additional SD of pupil dilation, the odds of TI increased by 51% for T1 (odds ratio, 1.51; 95% CI, 1.12-2.03), by 31% for T2 (odds ratio, 1.31; 95% CI, 1.08-1.59), and by 49% for T3 (odds ratio, 1.49; 95% CI, 1.13-1.97). The intervention significantly reduced TI (risk reduction, 31.5%; 95% CI,

(continued)

Key Points

Question How do physicians handle uncertainty when making live therapeutic decisions?

Findings In this randomized clinical trial of 34 neurologists from Canada, an educational intervention showed a significant 31% reduction in therapeutic inertia compared with the control group. Pupil dilation, a marker of autonomic arousal, mediated the effect of the educational intervention on therapeutic inertia.

Meaning In this study, the educational intervention helped facilitate optimal treatment choices by decreasing therapeutic inertia in neurologists by reducing autonomic arousal responses; further study in other specialties is warranted.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

16.1%-47.0%). Autonomic arousal responses mediated 29.0% of the effect of the educational intervention on TI.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, the TLS intervention decreased TI as measured by pupil dilation, which suggests that individual autonomic arousal is an indicator of how physicians handle uncertainty when making live therapeutic decisions. Pupil response, a biomarker of TI, may eventually be useful in medical education.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03134794

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Introduction

Therapeutic decision-making requires an individualized balance of the safety and efficacy profiles of different agents with either imperfect information or uncertain response of that choice.[1,2] One outcome in decision-making in the context of uncertainty is therapeutic inertia (TI). Therapeutic inertia is characterized by suboptimal decision-making not to initiate or intensify treatment when treatment goals are unmet.[3-5] Therapeutic inertia affects 60% to 90% of physicians caring for patients with chronic conditions (eg, hypertension, diabetes, or multiple sclerosis [MS]).[4-7] Suboptimal decision-making is associated with worse clinical outcomes and higher health care costs.[3-5,8] A randomized clinical trial on MS care reported a 70% reduction of TI in neurologists, using a short (<5 minutes) and simple (application of the traffic light system [use of established associations between traffic light colors and actions to stop or proceed]) educational intervention.[9] For MS care, overcoming TI corresponds to appropriately switching from a first-line agent (eg, glatiramer or interferon) to a high-efficacy treatment (eg, fingolimod or monoclonal antibodies) when given both clinical and radiologic evidence of disease progression.[9-13]

Recent studies reported that decision-making in the context of uncertainty is associated with autonomic arousal, as measured by pupil dilation.[14,15] In particular, phasic pupil size increases are associated with suboptimal or erroneous decision-making involving high uncertainty.[16,17] However, the association between autonomic arousal and therapeutic decision-making in the context of uncertainty is unknown. A better understanding of pupil dilation as a marker of an autonomic arousal response and TI may facilitate the development of decision-aid tools or other educational interventions to overcome suboptimal or erroneous decision-making in the context of other chronic medical conditions (ie, hypertension, diabetes, and dyslipidemia).

In this randomized clinical trial, we investigated (1) the relation between autonomic arousal responses and TI, (2) how a previously tested and effective educational intervention[9] affects autonomic arousal responses and TI, and (3) whether autonomic arousal responses mediate the association between the educational intervention and TI. We used MS care as an appropriate model for complex therapeutic decision-making arising in the management of chronic medical conditions using a previously tested and effective educational intervention to reduce TI.[9] Consistent with the details in the protocol for the Canadian study, we hypothesized that our educational intervention would decrease practitioner uncertainty about therapeutic choices, as reflected in decreased autonomic arousal responses, and thereby lead to an improvement in therapeutic decision-making.[14,16,17]

Methods

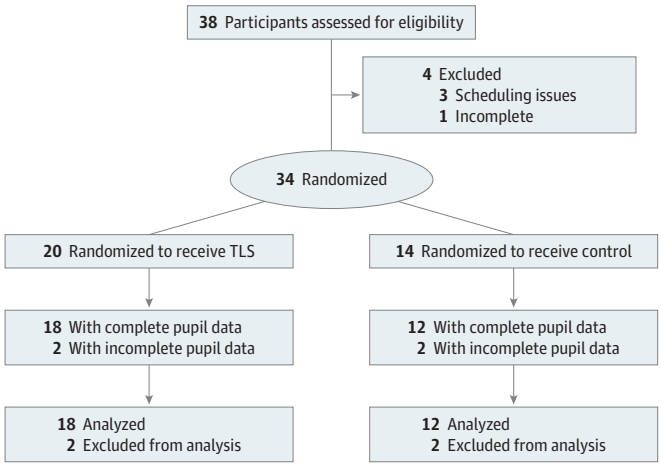
Study Design

In the initial study conducted in Argentina, 90 neurologists who provided care to patients with MS were randomly assigned to the TLS intervention (n = 45) or to the control group (n = 45). A 70% reduction in TI after the TLS intervention was found compared with controls (odds ratio, 0.30; 95% CI, 0.10-0.89). In the present study using a similar design, we added the assessment of pupil responses to determine how the TLS would decrease uncertainty and TI. We conducted a randomized clinical trial of MS experts and general neurologists who care for patients with MS practicing at 15 outpatient MS clinics in academic and community institutions from across Canada. We randomly assigned participants to an educational intervention group or to a usual care control group from December 2017 to March 2018. The educational intervention used the traffic light system (TLS) to reduce TI in the management of MS. The control group made therapeutic decision-making without being exposed to the TLS intervention, in line with current standard practice. Randomized group assignment and allocation concealment were controlled by Qualtrics. Participants were not aware to which group they were randomized. Investigators were also blinded to the treatment allocation. The mean (SD) time of study completion was 44.9 (6.7) minutes and participants received CAD$450 (equivalent to $350). The trial protocol is available in Supplement 1. The protocol was amended on October 25, 2017, to add pupil measures as a primary outcome. This amendment was approved by the Research Ethics Board of St Michael's (which became Unity Health Toronto in May 2018). Data were analyzed from September 2018 to March 2020. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials. Details are available at ClinicalTrials.gov (NCT03134794) and elsewhere.[9]

Inclusion Criteria and Participants

Neurologists actively caring for patients with MS across Canada were invited to participate by email sent from the Canadian Network of MS Clinics and NeuroSens (Lind Publishing Inc) (**Figure 1**). These networks comprise most MS neurologists in Canada. Participants were recruited from December 13, 2017, to March 2, 2018. Participants who completed a postresidency MS fellowship were classified as *MS specialists*. Physicians seeing less than 1 patient with MS per month were excluded from the study. Participants provided written informed consent. The study was approved by the Research Ethics Board of St Michael's Hospital, University of Toronto.

Figure 1. CONSORT Flow Diagram



TLS indicates traffic light system (use of established associations between traffic light colors and actions to stop or proceed).

Educational Intervention

The Traffic Light System

We applied a previously proven effective TLS intervention[9] to facilitate the identification of patients at high risk of disease progression (based on clinical and imaging evidence of disease progression) introduced by case scenarios. The TLS supports the decision-making process by use of established associations between traffic light colors and actions to stop or proceed.[9,18-20] For example, in the context of this intervention, a red light represents high risk and triggers a *stop and think* action, whereas a green light represents low risk and a triggers a *continue the same strategy* action. A previous study reported that the TLS can interrupt automatic behavior and lead to more optimal decision-making.[21] In our MS care model, the TLS aims for the red traffic light to indicate a warning sign of disease progression and a switch from a low-efficacy agent (eg, interferon or glatiramer) to a more effective disease modifying treatment (eg, monoclonal antibodies).[10-12] The TLS aims for the green traffic light to indicate stability in a patient and following a good clinical course (eg, no relapse and stable activity on brain imaging), therefore requiring no immediate therapeutic changes.

Data Collection and Study Flow

The study progressed as follows: (1) collection of demographic and practice-based information from participants, (2) participant completion of behavioral experimental procedures, and (3) participant completion of 20 simulated and standardized case scenarios (10 before and 10 after the intervention). We used simulated case scenarios reflecting common situations in clinical practice that were previously designed and validated by our research team (G.S. and J.O.) and MS experts, 16 of whom directly assessed the presence of TI.[9] All simulated case scenarios were presented auditorily (via headphones connected to the computer) to avoid interference of visual stimulation and automatic eye movements with pupil responses. The mean (SD) duration of case scenarios was 35.4 (7.1) seconds (range, 27-50 seconds). For each simulated case scenario, we identified 3 periods during which critical information was provided (eTable 1 in Supplement 2). The first period (T1) provided critical clinical information (present and previous clinical relapses, type of relapse, and/or symptoms). The second period (T2) informed about the neurological status of the patient (Expanded Disability Status Scale). The third period (T3) provided critical brain imaging information (number and nature of new lesions, gadolinium-enhancing lesions). The period before the start of case scenarios (T0) served as baseline, while the fourth period (T4) represented the final segment in which standardized questions (eg, "What would you do? Please select one of the options") were asked in preparation to the treatment options (**Figure 2**A). Compared with the baseline T0, we expected an autonomic arousal response during critical information periods T1 through T3 and little response during T4.

Based on previously reported associations of risk and ambiguity aversion with TI,[6,7] we considered also their relation to autonomic arousal responses and TI, using established measures in the financial domain.[22,23] Briefly, ambiguity aversion is defined as a dislike for events with unknown probability compared with events with known probability.[22]Ambiguity aversion was assessed asking participants to choose between a known 50/50 option (an urn with equal number of blue and red balls) providing $400 or $0 and an option with unknown probability of the same outcomes. Risk aversion was assessed by asking participants to indicate the minimal certain payoff they would prefer over a gamble with a 50/50 chance of winning $400 or $0[6] (eAppendix in Supplement 2).

Outcome Measures

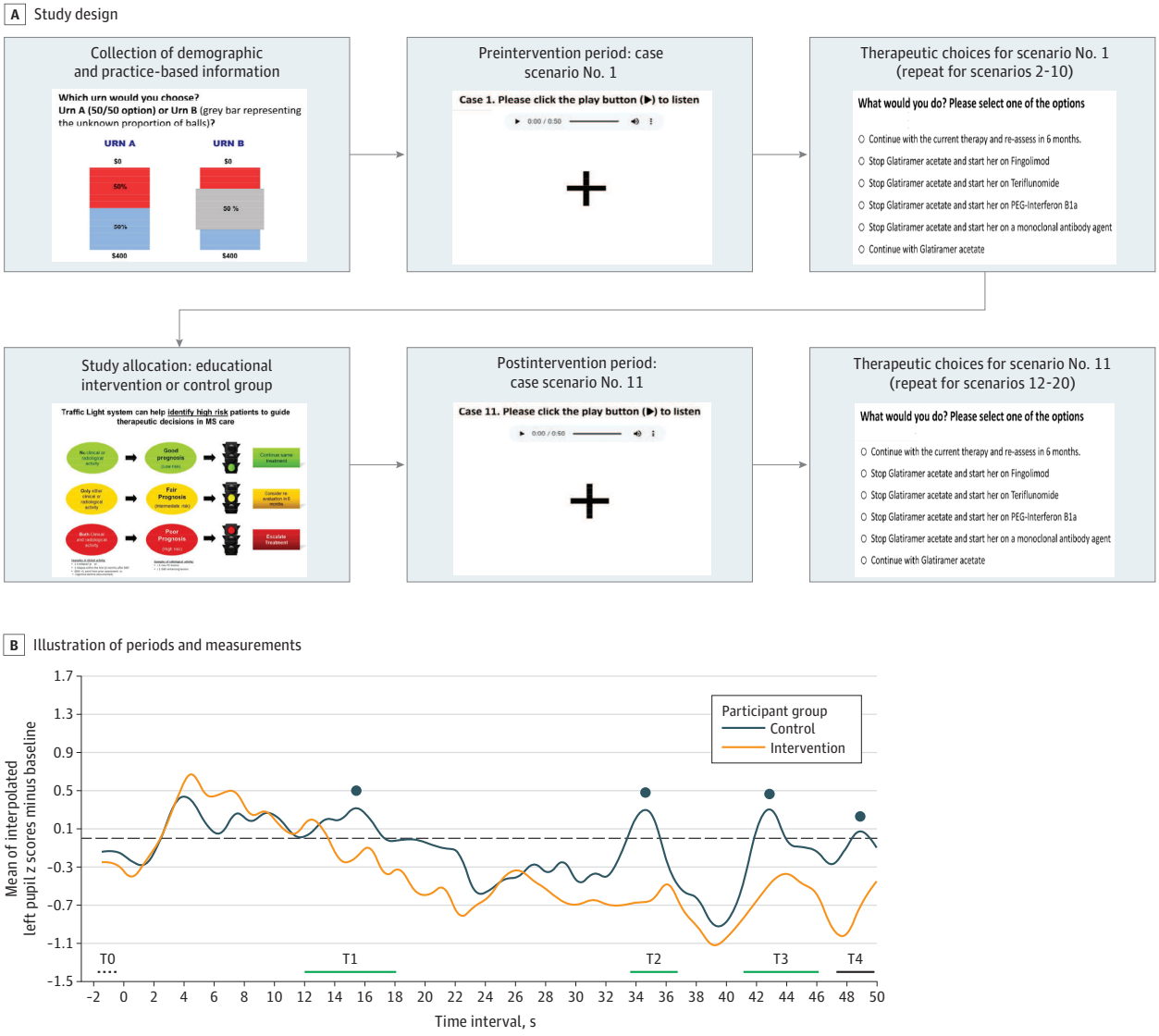
Therapeutic inertia is defined as lack of treatment escalation despite evidence of disease progression. We defined disease progression as the combination of a clinical relapse plus the presence of 5 or more new lesions (T2 or fluid-attenuated inversion recovery sequences) or at least 1 gadolinium-enhancing lesion in follow-up magnetic resonance imaging scans.[10,11] Using the combination of clinical relapse and magnetic resonance imaging activity is consistent with evidence regarding the risk of treatment failure in patients receiving interferon beta.[24] For each of our case scenarios, we determined TI as a binary variable (present vs absent; primary outcome). A secondary

outcome included TI greater than or equal to 25% of responses, meaning that participants did not escalate treatment when recommended in at least 1 of 4 simulated case scenarios.[9-12]

Experimental Procedures

The study was conducted in an ambulatory clinic–type setting to increase ecological validity. Room temperature, light conditions (100 lumens), and participant sitting positions were held constant. We calculated *z* scores for pupil time-series scored within each participant to allow comparison of pupil dilation between and within simulated case scenarios, critical periods, and participants. The mean pupil size (measured at T0, ie, 1500 ms - 500 ms before scenario onset) was taken as pupil baseline.[25] For each simulated case scenario, we estimated autonomic arousal responses by

Figure 2. Study Design and Time Period Illustration



A, Participants answered demographic and practice-based questions and provided risk and ambiguity preferences. Next, they listened to simulated case scenarios. Each scenario was followed by 6 therapeutic choices, which remained on the screen until the participant selected 1 of them. After the first 10 simulated case scenarios (pre-intervention), participants were randomized to the intervention or the control group. All participants performed another 10 simulated case scenarios. B, The black dots represent the peak pupil size within each period used to compute pupil responses (pupil peak for each period minus mean baseline at period 0 (T0). Peaks were determined similarly for both groups across all periods and case scenarios. T1 indicates first period (critical clinical information); T2, second period (neurological status of the patient); T3, third period (critical brain imaging information); and T4, fourth period (standardized questions were asked).

subtracting the mean baseline pupil diameter from the peak pupil dilation during each critical period (T1-T3) (Figure 2B).[15,26] Further details are available in the eAppendix in Supplement 2.

Sample Size

Our study was underpowered to evaluate differences in TI between groups.[9] The observed 15.5% absolute difference between groups (unadjusted results)[9] would require a sample size of a minimum of 78 participants per group with an $\alpha = .05$ and $\beta = .2$. The power to determine differences in phasic pupil response in relation to TI was 99%.

Statistical Analysis

We applied 3 analytical approaches: (1) comparison of autonomic arousal responses across critical periods, (2) treatment-effect analysis evaluating the association between autonomic arousal responses and TI, and (3) a mediation analysis to assess how the association between individual participant characteristics and TI may be mediated by autonomic arousal responses. For the first approach, we used nonparametric tests (Wilcoxon rank sum test for continuous variables and Mann-Whitney test for categorical variables). For the second approach, we compared high vs low arousal between groups stratified by intervention period (preintervention vs postintervention). We used generalized estimating equations to assess relationships between the variables of interest with TI accounting for clustering (repeated observations on participants) across all TI scenarios for each time period. This analysis controlled for the predefined explanatory variables age, specialist status (MS expert vs general neurologist), years of practice, risk preferences, and ambiguity aversion as identified in previous research.[6] To test the treatment effect of the educational intervention (TLS), we used difference-in-differences models (also called untreated control group design with pretest and posttest).[27] This model allowed us to measure the treatment effect of our intervention by comparing the change over time (posttest minus pretest performance) between the intervention and control group. For the third approach, pupil dilation for each participant and case scenario was tested as a mediator. Thus, the mediation analysis evaluated whether individual autonomic arousal responsivity accounted for the benefits of the educational intervention on TI. Mediation analysis is a technique commonly used in the social sciences to explain a relationship between an independent variable (eg, demographic variables) and an outcome via a third variable (called *mediator*).[28,29] We measured whether the effect of our intervention on TI was mediated by pupil-indexed autonomic arousal.

All tests were 2-tailed, and $P < .05$ wase considered significant. We used Stata version 13 (StataCorp LLP) and SAS version 9.4 (SAS Institute Inc) to conduct all analyses.

Results

Participant Characteristics

Of 38 eligible participants, 34 (89.4%) neurologists completed the study. The mean (SD) age was 44.6 (11.6) years; 38.3% were female and 20 (58.8%) were MS specialists. Participants had a mean (SD) of 12.5 (12) years of experience and assessed a mean (SD) of 23.1 (16) patients with MS per week. Of the 34 participants who completed the study, pupillary data were available in 30 (88.2%) participants. Two participants in each group had incomplete or missing pupil data (Figure 1). **Table 1** presents baseline characteristics of the study population.

Participants showed risk-neutrality in our measures of risk attitudes and the minimal safe amounts participants preferred over the 50/50 gamble did not differ between groups (Mann-Whitney $P = .14$; mean [SD] control: $175.7 [$45.2]; mean [SD] intervention: 211 [78.8]). Nineteen (55.9%) participants showed aversion to ambiguity in the financial domain. There was no difference in baseline pupil data between groups for each simulated case scenario (2.82 mm vs 2.96 mm; Mann-Whitney $P = .57$).

TI was present in 50.0% (17 of 34) of participants in at least 1 case scenario, representing 7.7% (42 of 544) of all individual responses that assessed TI. Non-MS experts had higher prevalence of TI compared with MS experts (11.5% vs 5.2%; $P = .01$).

Arousal Responses and TI

Overall, pupil size increased for each period relative to baseline (F test of overall significance indicating whether a linear regression model provides a better fit to the data than a model that contains no independent variables, all $P < .001$). The results remained robust after adjustment for the prespecified covariates ($P < .001$).

The multivariate analysis adjusted for age, sex, MS expertise, risk preferences, ambiguity aversion, preintervention vs postintervention period, and intervention group by period (**Table 2**) showed that pupil dilation was positively related to TI for all critical periods (T1 to T3). For every additional SD of pupil dilation, the odds of TI increased by 51% for T1 (odds ratio, 1.51; 95% CI, 1.12-2.03), by 31% for T2 (odds ratio, 1.31; 95% CI, 1.08-1.59) and by 49% for T3 (odds ratio, 1.49; 95% CI, 1.13-1.97). As expected, there was no association between pupil dilation and TI for T4 (odds ratio, 1.07; 95% CI, 0.86-1.34) as no critical information was provided, which may suggest a relation between TI and the arousal elicited by critical clinical information.

Our results were robust to using secondary outcome measures (Table 2). Together, stronger autonomic arousal responses at critical periods were associated with stronger TI. For TI equal to or greater than 25%: for T1 (OR, 1.53; 95% CI, 1.11-2.12), for T2 (OR, 1.33; 95% CI, 1.07-1.63), for T3 (OR, 1.51; 95% CI, 1.13-2.00).

Table 1. Baseline Characteristics of Participants

Characteristic	No. (%)		
	Total (N = 34)	Control (n = 14)	Intervention (n = 20)
Age, mean (SD), y	44.6 (11.6)	40.5 (8.5)	47.5 (13.5)
Female sex	13 (38.2)	6 (42.9)	7 (35.0)
Practice characteristics			
MS specialists	20 (58.8)	6 (42.9)	14 (70.0)
General neurologists who care for patients with MS	14 (41.2)	8 (57.1)	6 (30.0)
Practice setting: academic hospitals	28 (82.4)	6 (42.9)	14 (70.0)
Years in practice, mean (SD)	12.5 (11.8)	9.4 (9.5)	14.7 (12.9)
≥20 Patients with MS seen per week	15 (44.1)	4 (28.6)	11 (55.0)
Author of a peer-reviewed publication in the last 12 mo	22 (64.7)	10 (71.4)	12 (60.0)
Risk preference, minimal safe amount, mean (SD), $[a]	196.5 (68.5)	175.7 (45.2)	211 (78.8)
Ambiguity aversion[b]	19 (55.9)	8 (57.1)	11 (55.0)
Pupil data, mean (SD), mm[c]			
Pupil size			
Baseline[d]	2.90 (0.87)	2.82 (0.35)	2.96 (0.99)
Peak[e]	3.27 (1.10)	3.15 (0.5)	3.35 (1.35)
Response (peak minus mean baseline)[c]	1.60 (1.42)	1.69 (1.34)	1.54 (1.47)

[a] Risk preference was assessed by asking participants to indicate the minimal certain payoff they would prefer over a gamble with a 50/50 chance of winning $400 or $0.

[b] Ambiguity aversion is defined as a dislike for events with unknown probability compared with events with known probability. Ambiguity aversion was assessed asking participants to choose between a known 50/50 option (an urn with equal number of blue and red balls) providing 400 or 0 dollars and an option with unknown probability of the same outcomes.

[c] Pupil data were available for 30 participants. Pupil data reflect means across the study after interpolation and calculation of z score.

[d] There were no differences in baseline characteristics between groups.

[e] Only including critical periods: the first, in which clinical presentation was provided, the second, in which functional status was provided, and the third, in which magnetic resonance imaging findings were provided.

Table 2. Relationship Between Pupil Dilation by Critical Periods and Therapeutic Inertia

Outcome: therapeutic inertia	OR (95% CI)				
	Model for T1 (clinical presentation)	Model for T2 (functional status)	Model for T3 (MRI findings)	Model for T4 (standardized question)	Aggregated results for T1-T3
Maximum pupil dilation minus baseline for TI indicator	1.51 (1.12-2.03)	1.31 (1.08-1.59)	1.49 (1.13-1.97)	1.07 (0.86-1.34)	1.47 (1.24-1.74)
Maximum pupil dilation minus baseline for TI >25%	1.53 (1.11-2.12)	1.33 (1.07-1.63)	1.51 (1.13-2.00)	1.08 (0.86-1.36)	1.49 (1.19-1.87)

Abbreviations: MRI, magnetic resonance imaging; OR, odds ratio; T1, first period; T2, second period; T3, third period; and T4, fourth period.

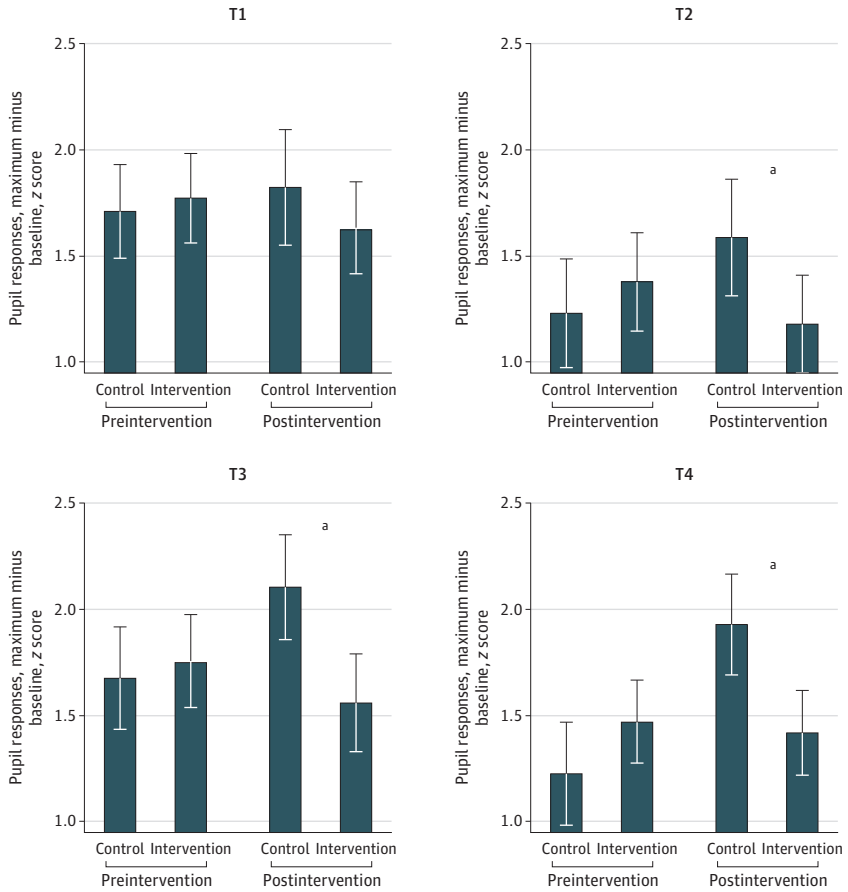
Group Allocation and Autonomic Arousal Responses

Pupil size did not differ significantly between the TLS and control groups before the intervention but did so after the intervention for T2, T3, and T4 (**Figure 3**). Overall, the multivariate analysis showed that in the postintervention period, participants in the control group had significantly enlarged pupils (as a continuous variable) compared with the intervention group for T2 (β, −0.46; 95% CI, −0.90 to −0.01; *P* = .049), T3 (β, −0.63; 95% CI, −1.04 to −0.22; *P* = .004), and T4 (β, −0.75; 95% CI, −1.12 to −0.37; *P* < .001) (eTables 2 and 3 in Supplement 2). No difference was observed for T1 (β, −0.23; 95% CI, −0.64 to 0.19; *P* = .47). The adjusted analysis for the dichotomized pupil response (maximum-peak minus mean-baseline ≥0.1 difference in *z* score as a high autonomic arousal vs <0.1 difference in *z* score low autonomic arousal response) showed similar results (hazard ratio control [reference category], 10.1 [95% CI, 8.2-12.0] vs hazard ratio TLS, 7.2 [95% CI, 6.2-8.1] vs LR control, 4.5 [95% CI, 1.6-7.5] vs LR TLS, 3.2 [95% CI, 0.8-5.5]; *P* < .01]) (eFigure 1 in Supplement 2). Together, these data suggest that the educational intervention has a protective effect, which extends into the period when participants made decisions in the context of uncertainty.

Educational Intervention and TI

In a previous study,[9] the educational intervention showed a significant reduction in TI. To assess the presence of a treatment effect on individual TI, we used the difference-in-differences analytical strategy (eTable 2 in Supplement 2). We found that participants in the educational intervention group had a significant reduction in TI (risk reduction, 31.5%; 95% CI, 16.1%-47.0%) compared with the control group (eFigure 2 in Supplement 2). Linear regression analysis adjusted for participant age, sex, expertise, risk preference, and pupil dilation showed that for every therapeutic decision, there

Figure 3. Effects of Intervention and Group Randomization on Pupil Responses



Pupil-linked autonomic arousal responses (peak minus mean baseline) are shown separately for intervention and control groups, stratified by the intervention period. Lower responses in the intervention group extend to T4, in which no critical information was provided, which may suggest that the protective effect of the intervention extends into the period when participants made decisions in the context of uncertainty. T1 indicates first period (critical clinical information); T2, second period (neurological status of the patient); T3, third period (critical brain imaging information); and T4, fourth period (standardized questions were asked).

[a] *P* < .01 for the comparison of pupil responses between control and intervention groups.

was a significant TI decrease of 5.0% (−5.0%; 95% CI, −0.8% to −9.3%) in the intervention group. There was no interaction between the education intervention and MS expertise (β, −0.518; 95% CI, −3.936 to −2.901; P = .23). The difference-in-differences analysis revealed no evidence for confounding endogenous effects (eTable 4 in Supplement 2). Together, these data replicate the previous findings that the TLS intervention reduces TI.[9]

Autonomic Arousal Response, Mediation, Educational Intervention, and TI

Autonomic arousal responses mediated 29.0% of the total effect of the educational intervention on TI (eFigure 3 in Supplement 2). The direct effect of the educational intervention on TI was −3.5% (95% CI, −9.2% to 3.5%). Other factors (eg, age, sex, risk preference) had a nonsignificant or a negligible effect. Further details are in the eAppendix in Supplement 2.

Discussion

To date, the role of autonomic arousal for therapeutic decision making remains unexplored. In the present study, we addressed this gap in the framework of therapeutic MS care decision-making, with a focus on decisions not to escalate treatment when recommended by best practice guidelines (ie, TI). We analyzed pupil dilation as a marker of autonomic arousal[14,15] and found that both continuously measured pupil dilation and dichotomized high vs low pupil responses were associated with TI. For every additional SD of pupil dilation, the odds of TI increased by 31% to 51% depending on the clinical information being provided. Even though our study had low statistical power and Canadian neurologists show comparatively little TI,[7] we estimated that participants in the control group would have reduced TI by almost a third if they would have been randomized to the intervention group. Our data suggest that the intervention may ameliorate TI by reducing autonomic arousal responses to critical information. Pupil dilation mediated the effects of the educational intervention on TI (explaining 29% of the total mediated effect).

Physician uncertainty may be a factor in rapid pupil-linked autonomic arousal responses, affecting behavioral choices[14] and the updating of beliefs with presented evidence.[30] Our educational intervention may reduce autonomic arousal by reducing uncertainty and thereby facilitating alternative behavioral strategies. Specifically, the warning function of a red traffic light may help emphasize the need for switching to a more effective agent [9] and may concurrently boost the physician's confidence in the therapeutic decision.

Relevance for Clinical Practice

Therapeutic inertia commonly affects physicians caring for patients with chronic medical conditions such as MS, diabetes, and hypertension.[31-33] This study may help increase the understanding of how physicians make therapeutic decisions in the context of uncertainty. Critical clinical information increases autonomic arousal and stronger autonomic arousal responses are associated with suboptimal therapeutic decision-making (ie, TI). Moreover, the inertia-reducing effects of our educational intervention appear to be mediated by reduced autonomic arousal responses. We may now be able to identify physicians who are making frequent suboptimal decisions (>25%) and to estimate potential reductions in TI from novel educational interventions. Furthermore, autonomic arousal responses may serve as a marker of the effectiveness of those education interventions. This marker is unaffected by demand effects or cognitive biases. Consequently, our findings may help create other avenues to tailor educational interventions and formal risk-assessment training to decision-makers (medical students, family doctors, and specialists). This approach may help optimize treatment decisions for other more prevalent chronic diseases and lead to improved medical education and better patient outcomes.

Limitations

This study has limitations. First, pupil size is not a standard measure in clinical practice. Second, autonomic arousal responses may have different triggers and effects than the ones we tested. Third, given our small sample size, imbalances between groups may lead to residual confounding. We used a statistical approach (eg, generalized estimating equations and mixed models) to address these imbalances. Fourth, simulated case scenarios may not truly reflect therapeutic decision-making in clinical practice. Fifth, the TLS we used is just 1 example of an intervention suitable for MS care. Other interventions may be needed and more effective for the management of other prevalent acute and chronic conditions.

Despite these limitations, our conclusions are strengthened by a randomized intervention design showing an autonomic arousal–mediated link between an effective therapeutic intervention and therapeutic decision-making made by physicians who care for patients with MS (eFigure 3D in Supplement 2).

Conclusions

Therapeutic inertia is a common phenomenon in clinical care, associated with worse outcomes and higher health care costs.[6,8,34] The TLS education intervention appeared to help facilitate optimal therapeutic choices by ameliorating the uncertainty associated with clinical information and decreasing TI. Autonomic arousal responses represent therapeutic uncertainty, which was significantly decreased among physicians randomized to the TLS intervention. Our findings may have practical implications for medical education, therapeutic decision-making, and patient outcomes.

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Corresponding Author: Gustavo Saposnik, MD, MPH, PhD, Division of Neurology, Department of Medicine, St Michael's Hospital, University of Toronto, 55 Queen St E, Toronto, ON M5C 1R6, Canada (gustavo.saposnik@unityhealth.to).

Author Affiliations: Division of Neurology, Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Saposnik, Oh, Terzaghi, Kostyrko); Zurich Center for Neuroeconomics, Department of Economics, University of Zurich, Zurich, Switzerland (Saposnik, Grueschow, Ruff, Tobler); Clinical Outcomes and Decision Neuroscience Unit, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Saposnik); Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Saposnik, Terzaghi, Vaidyanathan, Nisenbaum); Applied Health Research Centre, Centre for Urban Health Solutions, St Michael's Hospital, Toronto, Toronto, Ontario, Canada (Nisenbaum).

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Concept and design: Saposnik, Ruff, Tobler.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Saposnik, Grueschow, Terzaghi, Kostyrko, Nisenbaum, Ruff, Tobler.

Critical revision of the manuscript for important intellectual content: Saposnik, Grueschow, Oh, Vaidyanathan, Nisenbaum, Ruff, Tobler.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
eAppendix. Procedures, Pupil Data Processing, and Statistical Analysis
eTable 1. Critical Time Periods and Duration of Simulated Case-Scenarios

eTable 2. Effect of Group on Pupil Dilation: Difference-in-Difference Analysis
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eFigure 2. Treatment Effects Using Difference-in-Differences
eFigure 3A. Schematic Representation of the Mediation Analysis
eFigure 3B. Schematic Representation of the Mediation Analysis Derived From the Structural Equation Modelling in MS Care Graph
eFigure 3C. Structural Equation Model Used for Mediation Analysis
eFigure 3D. Proposed Pathways Associated With Therapeutic Inertia in MS Care
eTable 3. Differences in Pupil Responses Among Time Periods
eTable 4. Assessment of Endogenous Effects for Each Model According to Each Critical Time Period

SUPPLEMENT 3.
Data Sharing Statement